CARDIOVASCULAR, PHARMACOLOGY, CHEMISTRY

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THE COUNCIL FOR TOBACCO RESEARCH - U.S.A

633 THIRD AVENUE
NEW YORK, N. Y. 10017

COMMITTEE:
Dr. Cattell, Chm.
Dr. Jacobson
Dr. Bing

Application For Research Grant

Date:

1. Name of Investigator(s): (include Title and Degrees) Herbert McKennis, Jr., Ph.D., Professor of Pharmacology

2. Institution & Address: Medical College of Virginia, Richmond, Virginia 23219

3. Short Title of Project: Factors Controlling the Biological Disposition of Pyridine Compounds of Tobacco Smoke

4. Proposed Starting Date: July 1, 1967

5. Anticipated Duration of this Specific Study: 1967-1970 (3 years)

6. Brief Descripton of Objectives or Specific Aims:

From a series of experiments with support of the Council for Tobacco Research-U.S.A., it has been possible to describe the broad outlines of many of the routes involved in the mammalian metabolism of nicotine, nornicotine, and 3-acetylpyridine -- three of the many pyridine compounds that occur in tobacco and tobacco smoke. [The general nature of the previous studies are given in the publications which are enumerated in an attached list.] Through isolation or total synthesis it has been possible to supply many of the mammalian metabolites to biological investigators and to assist them in a variety of work on the pharmacological properties of many nicotine metabolites.

It is now desirable for us and interesting to us to expand our knowledge of the factors which determine the disposition of pyridine compounds arising from tobacco smoke and explore biochemical interactions between smoke components. There is already in the published literature some data that suggests that desensitization or tachyphylaxis to nicotine arises in part through a stimulation of the enzymes that are concerned with the metabolism of nicotine. It has been suggested that this stimulation of metabolism is produced by nicotine and that other substances have a similar capacity to enhance the metabolism of nicotine. Direct studies on nicotine metabolism are however very limited in their scope.

Through the current availability of synthetic routes to nicotine metabolites, which we have already described, and through synthetic routes which make possible the labelling of nicotine and related in almost any desired position, we believe that it is now possible to determine the nature of stimulation or inhibition of metabolism at almost all of the key points that are involved in mammalian systems. Similarly, it should be possible to determine individual differences in the capacity to metabolize nicotine and related pyridine compounds. (continued on sheet 1a attached)

7. Give a Brief Statement of your Working Hypothesis:

Current data on the effect of various smoke components on the metabolism and transfer of nicotine and other alkaloids are limited or apparently contradictory. A study of these factors should be helpful to an understanding of the biological effects of tobacco smoking.

6. Brief Description of Objectives or Specific Aims: (continued)

In the case of some of the simpler metabolites of nicotine, such as methylamine, it is relatively easy to obtain a broad picture of the nature of compounds which interfere with metabolic events. Work with ^{14}C-methylamine in our own laboratory (The Pharmacologist, Fall 1967, in press) and others illustrates that interference with oxidation of methylamine may be produced by some types of monoamine-oxidase inhibitors. The data suggest, however, that the inhibition may be referrable to a so-called methylamine oxidase which has not been fully characterized. Liver preparations obtained from rats after administration of monoamine-oxidase inhibitors have thus far been shown to be as fully capable as control livers in tests which involve a spectrophotometric measurement of the disappearance of nicotine. From another series of experiments, the data now suggests that the oxidation of nicotine can be impeded by the presence of large quantities of cotinine. It would be desirable to study possible effects of other pyridine compounds of smoke on the metabolism of nicotine and related substances. The need for a biologically oriented study appears to be re-emphasized by apparently conflicting chemical data on the oxidation of nicotine. For instance, the pyrolidine-N-oxide of nicotine has been considered (by J. C. Craig) to be the logical key intermediate in the biological formation of cotinine, while Linnell has reported that the same oxide in vitro inhibits the oxidation of nicotine to cotinine.

8. Details of Experimental Design and Procedures: (Attach Separate Pages)

With the aid of isotopically labelled nicotine and its metabolites it is feasible to study by a number of different methods factors influencing the disposition of nicotine. It is anticipated that during the current studies both in vivo and in vitro methods will be employed.

Initial experiments to determine the suitability of the rat as an experimental animal for initial studies have already been conducted. Liver microsomal preparations from both young and old rats of the Wistar strain have been examined for their capacity to metabolize nicotine in vitro. The general picture currently presented is that equivalent fractions by weight of liver that are obtained from older animals (250-550g body weight) do not metabolize nicotine as effectively as do the respective fractions from younger animals (150-175 g body weight). It is not currently known whether or not the observed deficiency in the older animals can be attributed to a lesser amount of metabolizing cellular fractions per unit of liver weight, or an overall lessening of metabolic ability that exists throughout the animal. It would be desirable to settle this point and to determine whether or not the elimination of unchanged nicotine by the older animals suffers any impairment. The additional matter of elimination can be settled without modification of the experimental design of the metabolic experiments. Questions of this type can be answered by comparing the ability of groups of young and old animals to metabolize

(continued on sheet 2a attached)

9. Physical Facilties Available (Where Other than Administering Organization Indicate Geographical Location)

Laboratories and animal facilities are located on the fourth and fifth floors of McGuire Hall at the Medical College of Virginia. Gas chromatography and isotope counting facilities are available in areas convenient to the working laboratories but separate from these. The equipment list includes a preparative ultracentrifuge, polarimeter, Warburg apparatus, hydrogenation apparatus, and the general equipment of chemical and biological laboratories.

10. Additional Requirements:

Additional requirements, if any, would depend upon the outcome of the research.

11. Biographical sketches of all principal and professional personnel (append)

12. List of publications: (Five most recent as pertinent) (append)

8. Details of Experimental Design and Procedures: (continued)

^{14}C-labelled nicotine and to eliminate unchanged alkaloid. For all of this isotopic material is now available as a result of our synthetic work and previous nutriculture: nicotine-^{14}C (random), nicotine-^{14}C-methyl, and nicotine-2-^{14}C. In addition, six of the mammalian metabolites of (-)-nicotine are available in both isotopic and non-isotopic form so that quantitative data can be obtained.

13. Budget: (1st year)

A. Salaries (Personnel by names)	% time	Amount
Professional		
Edward R. Bowman, Ph.D.	100%	R
Research Fellow (Ph.D. organic)	100%	
Technical		
Laboratory Assistant, B.S.	100%	
Laboratory Aide	100%	
Sub-Total:		
B. Consumable Supplies (list by categories)		
Chemical Reagents		2,200
Isotopes		1,500
Glass ware		800
Animals and feed		750
Sub-Total:		5,250
C. Other Expenses (itemize)		
Reprints and page charges		250
Travel (Presentation of reports at meetings and conferences)		500
Sub-Total		750
D. Permanent Equipment (itemize)		
Vacuum pumps (2)		550
		550
E. Overhead (15% of A+B+C)		5,955
Total:		46,205

Estimated Future Requirements:

	Salaries	Consumable Suppl.	Other Expenses	Permanent Equip.	Overhead	Total
Year 2	R R	5,500	1,000	1,000	6,675	52,175
Year 3		6,000	1,000	1,000	7,050	55,050

It is understood that the applicant and institutional officers in applying for a grant have read and found acceptable the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Signature [signature] Director of Project

644-9851 xt. 8153 Telephone

Signature [signature] Business Officer of the Institution

L. DANIEL COOKS VICE PRESIDENT – BUSINESS AND FINANCE Telephone

10035466643

Other Sources of Financial Support

List financial support for research from all sources, including own institution, for this and/or related research projects.

	Title of Project	Source	Amount	Duration
Current	Quantitative Methods for the Determination of the Distribution of Nicotine and Its Congeners in Biological Systems Institution supplies salary of principal investigator and all secretarial help currently obtained through other funds	American Medical Association Education and Research Foundation	$39,785.00	Expires January, 19[illegible]
Pending	None other than this application for the Council for Tobacco Research - U.S.A.			

Biographical Information

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HERBERT McKENNIS, JR.

R R R Attended elementary schools in Scarsdale, N.Y. and Loomis School, Windsor, Conn., Harvard S.B., R and Cornell Ph.D., R

Chemist at Nuodex Products Co., 1938-1939, and Ciba Pharmaceutical Products Co., 1940-1942.

Appointed Assistant in Biochemistry, Cornell University Medical College, 1942; Assistant Professor of Chemistry, Medical College of Virginia, 1945; Instructor in Physiological Chemistry, the Johns Hopkins University, 1946; Associate Professor of Biochemistry, Medical College of Virginia, 1948; Head, Basic Sciences Research Department, Naval C. E. Laboratory, 1949; Associate Professor, 1953, Professor of Pharmacology, Medical College of Virginia, 1955.

Biochemist; specialist in intermediary metabolism, antibiotics, alkaloids, polymeric compounds. U.S. and foreign patents: soil stabilization and antispasmodic.

Has done a wide variety of scientific advisory and technical consulting work for industrial firms, government agencies, scientific organizations, and universities.

Visiting Professor, University of Chile, 1960; Honorary member, Faculty of Medicine, University of Chile, Sociedad de Biologia de Santiago. Sigma Xi. Phi Lambda Upsilon.

American Chemical Society, American Society of Biological Chemists, The Society for Experimental Biology and Medicine, International Oceanographic Foundation, The New York Academy of Sciences, American Society for Pharmacology and Experimental Therapeutics, American Association for the Advancement of Science, Society of American Military Engineers, American Institute of Chemists, Virginia Academy of Science, Society of Toxicology.

Edward R. Bowman
Medical College of Virginia
Richmond, Virginia

Born: West Virginia 1927
Citizen U.S.A.

Education:

Concord College B.S. 1952 (Biology - Chemistry).

West Virginia University 1953 (Physiology).

Duke University 1955-56 (Graduate Student in Physiology).

Medical College of Virginia Ph.D. 1963 (Pharmacology).

Experience:

1961 - present	Research Associate Department of Pharmacology Medical College of Virginia Richmond, Virginia
1958 - 1961	Graduate Student, Major - Pharmacology Minor - Physiology & Biochemistry Medical College of Virginia Richmond, Virginia
1956 - 1958	Research Assistant Department of Pharmacology Medical College of Virginia Richmond, Virginia
1955 - 1956	Graduate Student, Major - Physiology Minor - Anatomy Duke University Durham, North Carolina
1954 - 1955	Bacteriologist State Department of Health Richmond, Virginia
1952 - 1953	Graduate Student, Physiology West Virginia University Morgantown, West Virginia
1952	Student, Biology & Chemistry Concord College Athens, West Virginia
1950 - 1951	U.S. Army
1947 - 1950	Student, Biology & Chemistry Concord College Athens, West Virginia
1944 - 1946	U.S. Army

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PUBLICATIONS

OF PROJECT WORK SUPPORTED BY

THE COUNCIL FOR TOBACCO RESEARCH - U.S.A.

1. Synthesis and properties of pyridylalanines.
   Herbert McKennis, Jr., and Edward R. Bowman.
   Virginia Journal of Science, 8, 314 (1957).

2. Metabolism of γ-(3-pyridyl)-γ-oxobutyric acid.
   Lennox B. Turnbull, Edward R. Bowman, and Herbert McKennis, Jr.
   Federation Proceedings, 17, 325 (1958).

3. γ-(3-Pyridyl)-γ-methylaminobutyric acid as a urinary metabolite of nicotine.
   Herbert McKennis, Jr., Lennox B. Turnbull, and Edward R. Bowman.
   Journal of the American Chemical Society, 79, 6342 (1957).

4. Metabolites of nicotine and a synthesis of nornicotine.
   Herbert McKennis, Jr., Lennox B. Turnbull, Harvey N. Wingfield, Jr., and Lovell J. Dewey.
   Journal of the American Chemical Society, 80, 1634 (1958).

5. The role of cotinine in nicotine metabolism
   Herbert McKennis, Jr., Lennox B. Turnbull, and Edward R. Bowman.
   Abstracts of Communications, IV. International Congress of Biochemistry, Vienna, Sept. 1-6, 1958.

6. A constant rate infusion apparatus.
   Quentin S. McKennis, Edward R. Bowman, and Herbert McKennis, Jr.
   Toxicology and Applied Pharmacology, 1, 61 (1959).

7. Metabolism of nicotine to (+)-γ-(3-pyridyl)-γ-methylaminobutyric acid.
   Herbert McKennis, Jr., Lennox B. Turnbull, and Edward R. Bowman.
   Journal of the American Chemical Society, 80, 6597 (1958).

8. Metabolism of nicotine in the human and excretion of pyridine compounds by smokers.
   Edward R. Bowman, Lennox B. Turnbull, and Herbert McKennis, Jr.
   The Journal of Pharmacology and Experimental Therapeutics, 127, 92 (1959).

9. Demethylation of cotinine in vivo.
   Herbert McKennis, Jr., Lennox B. Turnbull, Edward R. Bowman, and Einosuke Wada.
   Journal of the American Chemical Society, 81, 3951 (1959).

10. Oxidation of cotinine in vivo.
    Edward R. Bowman, Lennox B. Turnbull, and Herbert McKennis, Jr.
    Federation Proceedings, 18, 371 (1959).

11. Depressor activity from nicotine metabolites.
Edward R. Bowman, H. B. Kennedy, Jr., Einosuke Wada, and Herbert McKennis, Jr.
Abstracts of Communications, XXI. International Congress of Physiological Sciences, 41, Buenos Aires, August 9-15, 1959.

12. The isolation and structure of a ketoamide formed in the metabolism of nicotine.
Herbert McKennis, Jr., Edward R. Bowman, and Lennox B. Turnbull.
Journal of the American Chemical Society, 82, 3974 (1960).

13. Methylation in the metabolism of (-)-nicotine.
Lennox B. Turnbull, Edward R. Bowman, and Herbert McKennis, Jr.
Federation Proceedings, 19, 268 (1960).

14. The excretion and metabolism of nicotine.
Herbert McKennis, Jr.
Annals of the New York Academy of Sciences, 90, 36 (1960).

15. Norcotinine (desmethylcotinine) as a urinary metabolite of nornicotine.
Einosuke Wada, Edward R. Bowman, Lennox B. Turnbull, and Herbert McKennis, Jr.
Journal of Medicinal and Pharmaceutical Chemistry, 4, 21 (1961).

16. Depressor effects arising from (-)-cotinine.
Joseph F. Borzelleca, Edward R. Bowman, and Herbert McKennis, Jr.
The Pharmacologist, 2, 72 (1960).

17. Oxidation of nicotine-C-14 and nicotine-methyl-C-14 in vivo.
Lennox B. Turnbull, Einosuke Wada, Edward R. Bowman, and Herbert McKennis, Jr.
Federation Proceedings, 20, 172 (1961).

18. Metabolism of nicotine in the human.
Edward R. Bowman, Lennox B. Turnbull, and Herbert McKennis, Jr.
Virginia Journal of Science, 9, 438 (1948).

19. Degradation of (-)-cotinine in the human.
Herbert McKennis, Jr., and Edward R. Bowman.
Abstracts of Communications, V. International Congress of Biochemistry, Moscow, August 10-16, 1961, p. 393.

20. The mammalian degradation of (-)-nicotine to 3-pyridylacetic acid and other compounds.
Herbert McKennis, Jr., Edward R. Bowman, and Lennox B. Turnbull.
Proceedings of the Society for Experimental Biology and Medicine, 107, 145 (1961).

21. Metabolism of (-)-cotinine in the rat.
Sorell L. Schwartz, Edward R. Bowman, and Herbert McKennis, Jr.
Virginia Journal of Science, 12, 196 (1961).

22. Demethylation in the metabolism of (-)-nicotine.
Herbert McKennis, Jr., Lennox B. Turnbull, Sorell L. Schwartz, Einosuke Tamaki, and Edward R. Bowman.
The Journal of Biological Chemistry, 237, 541 (1962).

23. Metabolism of (-)-cotinine to a keto acid.
Sorell L. Schwartz, and Herbert McKennis, Jr.
Federation Proceedings, 21, 183 (1962).

24. Studies on the respiratory and cardiovascular effects of (-)-cotinine.
Joseph F. Borzelleca, Edward R. Bowman, and Herbert McKennis, Jr.
The Journal of Pharmacology and Experimental Therapeutics, 137, 313 (1962).

25. Studies on the metabolism of (-)-cotinine in the human.
Edward R. Bowman, and Herbert McKennis, Jr.
The Journal of Pharmacology and Experimental Therapeutics, 135, 306 (1962).

26. Routes in the mammalian metabolism of (-)-nicotine to 3-pyridylacetic acid.
Sorell L. Schwartz, Edward R. Bowman, and Herbert McKennis, Jr.
Abstracts of Papers, 16th Tobacco Chemists' Research Conference, Richmond, Virginia, Sept. 26-28, 1962, p. 7.

27. Studies on the metabolic fate of 3-acetylpyridine.
Lennox B. Turnbull, Edward R. Bowman, and Herbert McKennis, Jr.
Abstracts of Papers, 16th Tobacco Chemists' Research Conference, Richmond, Virginia, Sept. 26-28, 1962, p. 6.

28. The corrected structure of a ketoamide arising from the metabolism of (-)-nicotine.
Herbert McKennis, Jr., Lennox B. Turnbull, Edward R. Bowman, and Sorell L. Schwartz.
Journal of the American Chemical Society, 84, 4598 (1962).

29. N-Methylation of nicotine and cotinine in vivo.
Herbert McKennis, Jr., Lennox B. Turnbull, and Edward R. Bowman.
The Journal of Biological Chemistry, 238, 719 (1963).

30. Studies on the degradation of the pyrrolidine ring of (-)-nicotine in vivo. Formation of γ-(3-pyridyl)-γ-oxobutyric acid.
Sorell L. Schwartz, and Herbert McKennis, Jr.
The Journal of Biological Chemistry, 238, 1807 (1963).

31. The synthesis of hydroxycotinine and studies on its structure.
Herbert McKennis, Jr., Lennox B. Turnbull, Edward R. Bowman, and Einosuke Tamaki.
Journal of Organic Chemistry, 28, 383 (1963).

32. (-)-Cotinine.
Edward R. Bowman, and Herbert McKennis, Jr.
Biochemical Preparations, 10, 36 (1963).

33. Conjugate formation in the metabolism of 3-acetylpyridine.
Lennox B. Turnbull, Edward R. Bowman, and Herbert McKennis, Jr.
Abstracts of Papers, 17th Tobacco Chemists' Research Conference, Montreal, Quebec, Canada, Sept. 22-25, 1963, p. 11.

34. A comparative study of the metabolic release of methyl groups from a series of N-methylpyridinium compounds.
Herbert McKennis, Jr., Edward R. Bowman, Antonio Horvath, and John P. Bederka, Jr.
Nature, 202, 699 (1964).

35. Mammalian degradation of (-)-demethylcotinine.
Sorell L. Schwartz, and Herbert McKennis, Jr.
Nature, 202, 594 (1964).

36. Disposition and fate of (-)-cotinine-H^3 in the mouse.
Edward R. Bowman, Eskil Hansson, Lennox B. Turnbull, Herbert McKennis, Jr., and Carl G. Schmiterlöw.
The Journal of Pharmacology and Experimental Therapeutics, 143, 301 (1964).

37. Additional routes in the metabolism of 3-acetylpyridine.
Herbert McKennis, Jr., Lennox B. Turnbull, and Edward R. Bowman.
The Journal of Biological Chemistry, 239, 1215 (1964).

38. Effect of cotinine and other nicotine metabolites in vitro on duodenum and ileum segments.
K. S. Kim, Joseph F. Borzelleca, Edward R. Bowman, and Herbert McKennis, Jr.
Federation Proceedings, 23, 330 (1964).

39. The metabolic formation of γ-(3-pyridyl)-γ-hydroxybutyric acid and its possible intermediary role in the mammalian metabolism of nicotine.
Herbert McKennis, Jr., Sorell L. Schwartz, Lennox B. Turnbull, Einosuke Tamaki, and Edward R. Bowman.
The Journal of Biological Chemistry, 239, 3981 (1964).

40. Alternate routes in the metabolic degradation of the pyrrolidine ring of nicotine.
Herbert McKennis, Jr., Sorell L. Schwartz, and Edward R. Bowman.
The Journal of Biological Chemistry, 239, 3990 (1964).

41. Metabolism of 3-acetylpyridine to an analog of mandelic acid.
Lennox B. Turnbull, C. N. Lukhard, and Herbert McKennis, Jr.
Toxicology and Applied Pharmacology, 6, 362 (1964).

42. Disposition and fate of nicotine in animals.
Herbert McKennis, Jr.
Tobacco Alkaloids and Related Compounds, U. S. Von Euler, editor, Pergamon Press, Oxford, 1965, p. 53.

43. Urinary excretion of conjugate forms of 1-(3-pyridyl)ethanol after administration of 3-acetylpyridine.
Herbert McKennis, Jr., Lennox B. Turnbull, Edward R. Bowman, and C. Norman Lukhard.
The Journal of Biological Chemistry, 241, 1878 (1966).

44. The structure of dibromoticonine, a bromination product of nicotine.
Herbert McKennis, Jr., Edward R. Bowman, L. D. Quin, and R. C. Denney.
Abstracts of Papers, 152nd Meeting, American Chemical Society, New York, N. Y., Sept. 12-16, 1966.

45. Studies on the synthesis and metabolism of 4-(3-pyridyl)-4-methylaminobutyric acid-4-^{14}C.
Paolo L. Morselli, Edward R. Bowman, Helen H. Ong, and Herbert McKennis, Jr.
Virginia Journal of Science, 17, 345 (1966).

46. The fate and distribution of 1-(3-pyridyl)ethanol methiodide in relation to the toxicity of 1-(3-pyridyl)ethanol and 3-acetylpyridine.
John P. Bederka, Jr., Eskil Hansson, Edward R. Bowman, and Herbert McKennis, Jr.
Biochemical Pharmacology, 16, 1 (1967).

47. Studies on the separation of acidic metabolites of nicotine by gas chromatography.
Herbert McKennis, Jr., Edward R. Bowman, and Mohammad Saeed Dar.
Virginia Journal of Science, 18, 13 (1967).

48. Pharmacological action and intermediary role of 5-(3-pyridyl)tetrahydrofuranone-2.
Edward R. Bowman, Pavol Hrdina and Herbert McKennis, Jr.
Federation Proceedings, 26, 616 (1967).

49. Metabolism of (±)-Cotinine-2-^{14}C in the rat.
Paolo L. Morselli, Helen H. Ong, Edward R. Bowman, and Herbert McKennis, Jr.
Journal of Medicinal Chemistry, in press.

50. Methylamine metabolism in normal and mao-inhibitor-treated rats.
Paolo L. Morselli, Edward R. Bowman, and Herbert McKennis, Jr.
The Pharmacologist, in press.

51. On the congeners of whiskey.
Herbert McKennis, Jr., and Harvey B. Haag.
Journal of the American Geriatrics Society, 7, 848 (1959).

52. Depressor effects arising from (-)-cotinine.
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53. The excretion and metabolism of nicotine.
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54. The isolation and structure of a ketoamide formed in the metabolism of nicotine.
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55. Methylation in the metabolism of (-)-nicotine.
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56. L-γ-Glutamylhydrazine and the metabolism of hydrazine.
Herbert McKennis, Jr., Allan S. Yard, Elizabeth J. Adair, and J. H. Weatherby.
The Journal of Pharmacology and Experimental Therapeutics, 131, 152 (1961).

57. Demethylation in the metabolism of (-)-nicotine *in vivo*.
Herbert McKennis, Jr., Einosuke Wada, Edward R. Bowman, and Lennox B. Turnbull.
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58. Norcotinine (Desmethylcotinine) as a urinary metabolite of nornicotine.
Einosuke Wada, Edward R. Bowman, Lennox B. Turnbull, and Herbert McKennis, Jr.
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59. The isolation of 3-pyridylacetic acid, a urinary metabolite of (-)-cotinine.
Edward R. Bowman, Lennox B. Turnbull, and Herbert McKennis, Jr.
Abstracts of Papers, 14th Tobacco Chemists' Research Conference, Oct. 13-14, 1960, Winston-Salem, North Carolina.

60. Oxidation of nicotine-C^{14} and nicotine-methyl-C^{14} *in vivo*.
Lennox B. Turnbull, Einosuke Wada, Edward R. Bowman, and Herbert McKennis, Jr.
Federation Proceedings, 20, 172 (1961).

61. Inhibition by thyroxine of γ-aminobutyrate-α-ketoglutarate transaminase.
Antonio Horvath, Fernando Orrego, and Herbert McKennis, Jr.
Federation Proceedings, 20, 5 (1961).

62. Factors controlling the metabolism of γ-aminobutyric acid.
Antonio Horvath, Fernando Orrego, and Herbert McKennis, Jr.
The Journal of Pharmacology and Experimental Therapeutics, 134, 222 (1961).

63. Mammalian degradation of (-)-nicotine to 3-pyridylacetic acid and other compounds.
Herbert McKennis, Jr., Edward R. Bowman, and Lennox B. Turnbull.
Proceedings of the Society for Experimental Biology and Medicine, 107, 145 (1961).

64. Selective toxicity. (Book review).
Herbert McKennis, Jr.
Revista Medica de Chile, 88, 864 (1960).

65. Los oxoesteroides, el uso de hidrazidos fenólicos para su detección, caracterización y medición. (Book review).
Herbert McKennis, Jr.
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66. Metabolism of nicotine in the human.
Edward R. Bowman, Lennox B. Turnbull, and Herbert McKennis, Jr.
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67. Metabolism of (-)-cotinine in the rat.
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69. Aspects of the metabolism of isoniazid and acetylisoniazid in the human and the dog.
Allan S. Yard, and Herbert McKennis, Jr.
Journal of Medicinal and Pharmaceutical Chemistry, 5, 196 (1962).

70. Demethylation in the metabolism of (-)-nicotine.
Herbert McKennis, Jr., Lennox B. Turnbull, Sorell L. Schwartz, Einosuke Tamaki, and Edward R. Bowman.
The Journal of Biological Chemistry, 237, 541 (1962).

71. Inhibition of the catabolism of aspartic-4-C^{14} acid by thyroxine in vivo.
Antonio Horvath, and Herbert McKennis, Jr.
Enzymologia, 24, 91 (1962).

72. Studies on the metabolism of (-)-cotinine in the human.
Edward R. Bowman, and Herbert McKennis, Jr.
The Journal of Pharmacology and Experimental Therapeutics, 135, 306 (1962).

73. Metabolism of (-)-cotinine to a keto acid.
Sorell L. Schwartz, and Herbert McKennis, Jr.
Federation Proceedings, 21, 183 (1962).

74. The excretion and metabolism of triethylene glycol.
Herbert McKennis, Jr., Robert A. Turner, Lennox B. Trunbull, and Edward R. Bowman.
W. W. Muelder, M. P. Neidhardt, and Carl L. Hake.
Richard Henderson, Herbert G. Nadaeu, and Samuel Spencer.
Toxicology and Applied Pharmacology, 4, 411 (1962).

75. Studies on the respiratory and cardiovascular effects of (-)-cotinine.
Joseph F. Borzelleca, Edward R. Bowman, and Herbert McKennis, Jr.
The Journal of Pharmacology and Experimental Therapeutics, 137, 313 (1962).

76. Routes in the mammalian metabolism of (-)-nicotine to 3-pyridylacetic acid.
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77. Studies on the metabolic fate of 3-acetylpyridine.
Lennox B. Turnbull, Edward R. Bowman, and Herbert McKennis, Jr.
Abstracts of Papers, 16th Tobacco Chemists' Research Conference, Sept. 26-28, 1962, Richmond, Virginia, p. 6.

78. Acetylhydrazine as an intermediate in the metabolism of aroylhydrazines.
Lennox B. Turnbull, Allan S. Yard, and Herbert McKennis, Jr.
Journal of Medicinal and Pharmaceutical Chemistry, 5, 1327 (1962).

79. N-Methylation of nicotine and cotinine in vivo.
Herbert McKennis, Jr., Lennox B. Turnbull, and Edward R. Bowman.
The Journal of Biological Chemistry, 238, 719 (1963).

80. The synthesis of hydroxycotinine and studies on its structure.
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Journal of Organic Chemistry, 28, 383 (1963).

81. The corrected structure of a ketoamide arising from the metabolism of (-)-nicotine.
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Journal of the American Chemical Society, 84, 4598 (1962).

82. (-)-Cotinine.
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Biochemical Preparations, 10, 36 (1963).

83. Studies on the degradation of the pyrrolidine ring of (-)-nicotine in vivo. Formation of γ-(3-pyridyl)-γ-oxobutyric acid.
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The Journal of Biological Chemistry, 238, 1807 (1963).

84. Conjugate formation in the metabolism of 3-acetylpyridine.
Lennox B. Turnbull, Edward R. Bowman, and Herbert McKennis, Jr.
Abstracts of Papers, 17th Tobacco Chemists' Research Conference, Sept. 22-25, 1963, Montreal, Quebec, p. 11.

85. Metabolic release of methyl groups from a series of N-methylpyridinium compounds.
Herbert McKennis, Jr., Edward R. Bowman, Antonio Horvath, and John P. Bederka, Jr.
Nature, 202, 699 (1964).

86. Mammalian degradation of (-)-demethylcotinine.
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87. Disposition and fate of (-)-cotinine-H^3 in the mouse.
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88. Additional routes in the metabolism of 3-acetylpyridine.
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95. Urinary excretion of conjugate forms of 1-(3-pyridyl)ethanol after administration of 3-acetylpyridine.
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The Journal of Biological Chemistry, 241, 1878 (1966).

96. The structure of dibromoticonine, a bromination product of nicotine.
Herbert McKennis, Jr., Edward R. Bowman, L. D. Quin, and R. C. Denney.

Papers Published

During the Period of This Report

1. Urinary excretion of conjugate forms of 1-(3-pyridyl)ethanol after administration of 3-acetylpyridine.
Herbert McKennis, Jr., Lennox B. Turnbull, Edward R. Bowman, and C. Norman Lukhard.
The Journal of Biological Chemistry, 241, 1878 (1966).

2. The structure of dibromoticonine, a bromination product of nicotine.
Herbert McKennis, Jr., Edward R. Bowman, L. D. Quin, and R. C. Denney.
Abstracts of Papers, 152nd Meeting, American Chemical Society, New York, N. Y., Sept. 12-16, 1966.

3. Studies on the synthesis and metabolism of 4-(3-pyridyl)-4-methylaminobutyric acid-4-^{14}C.
Paolo L. Morselli, Edward R. Bowman, Helen H. Ong, and Herbert McKennis, Jr.
Virginia Journal of Science, 17, 345 (1966).

4. The fate and distribution of 1-(3-pyridyl)ethanol methiodide in relation to the toxicity of 1-(3-pyridyl)ethanol and 3-acetylpyridine.
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7. Metabolism of (±)-cotinine-2-^{14}C in the rat.
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Talks Given

During the Period of this Report

1. Studies on the synthesis and metabolism of 4-(3-pyridyl)-4-methylaminobutyric acid-4-^{14}C. Paolo L. Morselli, Edward R. Bowman, Helen H. Ong, and Herbert McKennis, Jr. Annual Meeting of the Virginia Academy of Science, Harrisonburg, Virginia, May 4-6, 1966.

2. The structure of dibromoticonine, a bromination produce of nicotine. Herbert McKennis, Jr., Edward R. Bowman, L. D. Quin, and R. C. Denney. 152nd Meeting, American Chemical Society, New York, N. Y., Sept. 12-16, 1966.

3. Some new synthetic routes to metabolites of nicotine. Herbert McKennis, Jr., Biological Seminar, Medical College of Virginia, Richmond, Virginia, Sept. 28, 1966.

4. Quantitative methods for the determination of the distribution of nicotine and its congeners in biological systems. Herbert McKennis, Jr., American Medical Association Workshop, Colorado Springs, Colorado, Nov. 1-3, 1966.

5. Studies on ^{14}C-labelled nicotine metabolites. Edward R. Bowman and Herbert McKennis, Jr., American Medical Association Workshop, Colorado Springs, Colorado, Nov. 1-3, 1966.

6. Pharmacological action and intermediary role of 5-(3-pyridyl)tetrahydrofuranone-2. Edward R. Bowman and Pavel Hrdina. 51st Annual Meeting of the Federation of American Societies for Experimental Biology, Chicago, Illinois, April 16-21, 1967.

7. Pharmacological effects of some nicotine metabolites and related compounds. K. S. Kim and J. F. Borzelleca, 51st Annual Meeting of the Federation of American Societies for Experimental Biology, Chicago, Illinois, April 16-21, 1967.

8. Pentafluropropionylation in the determination of nicotine. Herbert McKennis, Jr., S. C. Srivastava, and Edward R. Bowman. Annual Meeting of the Virginia Academy of Science, Roanoke, Virginia, May 6, 1967.